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VENTILATION AND VENTILATORY CONTROL IN HIGH ALTITUDE
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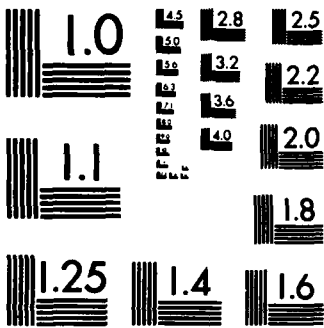


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VENTILATION AND VENTILATORY CONTROL IN
HIGH ALTITUDE PULMONARY EDEMA AND
ACUTE MOUNTAIN SICKNESS

FINAL REPORT

John T. REEVES, M.D.

April, 1983

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

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Summary

The present studies, done with the full consultation and collaboration of the Altitude Research Division at USARIEM, Dr. John T. Maher, Director, made potentially important contributions to our understanding of interaction of O_2 and CO_2 in the control of breathing, the development of new tests to predict ventilatory changes at high altitude, and a sensitive method for measuring the rate and magnitude of the acclimatization process. We also pointed to ethnic differences in ventilation between oriental and occidental subjects which could bear on adaptability of populations to high altitude.

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Foreword

This contract evaluated human ventilation at low and high altitude and therefore utilized Human Subjects. In the first study 14 Chinese and 14 western volunteers had measurements of ventilation, lung volumes, and blood gases. In the second study 14 other Caucasians had measurements at low altitude (Denver, 1600M) and 12 of these had measurements at Pike's Peak (4300M). All signed a human consent form previously approved by this institution and a U.S. Army Human Subject Review Committee. All subjects going to high altitude were shown, prior to exposure, to have no evidence of sickle cell trait. The only illness resulting from this study were the symptoms of headache, nausea, and vomiting (in 3 subjects) and malaise which occurred at high altitude. The possibility of high altitude illness was described in detail in the consent form. In no case was the symptomatology severe and all subjects completed the study protocol. Further the safety precautions outlined in the protocol and the consent form were carefully followed. Communication between civilian investigators and Army support personnel was excellent. The study was completed in the designated time with the collection of high quality data. For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.

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Report

The overall working hypothesis was that acute mountain sickness is a disorder of ventilatory mal-adaptation to high altitude. There were several sub-hypotheses and these are taken in order of work done.

Sub-hypothesis #1. Chinese, a population who appear to be particularly prone to altitude sickness, have ventilatory measurements at low altitude which may not be optimal for adjustment to high altitude. For example measurements published (in Chinese) from mainland China indicated that Chinese may have smaller lung volumes than expected for western subjects even when differences in body size are taken into account. The reports suggested that they also may have, compared to westerners, a high frequency, small tidal volume pattern of breathing and low ventilatory drives which might not be optimal at high altitude. Dr. S-Y Huang who was a visiting scholar from The Shanghai Academia Sinica, reviewed this literature for us. He also assembled 14 Chinese and 14 western males matched for body size to allow us to compare ventilatory measurements made in the same laboratory. The results confirmed that compared to westerners, the Chinese have higher respiratory frequencies, lower tidal volumes, lower alveolar ventilations, smaller lung capacities, and higher resting values of alveolar CO_2 . All of these differences if maintained at high altitude could impair the acclimatization process. In addition the Chinese had smaller ventilatory responses to inspired CO_2 , a finding of which the significance is not known for altitude adaptation. Thus the study confirmed that Chinese may not be well suited for life at high altitude and it may contribute to our understanding of their apparently high incidence of altitude sickness.

Sub-hypothesis #2. Those subjects who hypoventilate at high altitude can be predicted from measurements made at low altitude.

A. Low Altitude Tests. A major research effort, combining scientists from this Laboratory and from U.S.A.R.I.E.M. in Natick, examined subjects before and during a 5 day stay on Pike's Peak, Colorado, at the U.S. Army High Altitude Research Facility there. In the low altitude portion of the study we examined in these healthy volunteers the

interaction between hypoxia and CO_2 in driving the ventilation. A previously generally accepted concept was that hypoxia stimulates ventilation and hypocapnia or low CO_2 blocks the ventilatory response to hypoxia. Our findings were that the hypocapnia blunted the hypoxic response only in those persons who had relatively large ventilatory sensitivity to CO_2 . Persons with little ventilatory sensitivity had little or no inhibition of their ventilation during hypoxia. The important implication for high altitude is that a low CO_2 sensitivity could be a beneficial characteristic for persons adapting to high altitude and it could offset the potential disadvantage of a low ventilatory sensitivity to hypoxia. These findings were reported at the 1983 FASEB meeting and the abstract is given in the appendix (A).

B. Prediction of ventilation at high altitude. We found that the resting hypoxic ventilatory responses with CO_2 added to maintain the normal alveolar value done in Denver at 1600M predicted the resting ventilation which was measured on Pike's Peak at 4300M. The prediction was statistically significant on 3 of 5 days on Pike's Peak and was nearly significant on a 4th day. An exercise test was developed at low altitude where hypoxia was administered during exercise - without adding CO_2 - and ventilation was measured. The exercise test predicted well the ventilation during exercise on all 5 days at 4300M. These findings were reported at a recent meeting of the Western Society for Clinical Research, and the abstract is presented in the appendix (B).

C. We observed that total ventilation of subjects at high altitude included contribution not only of the acclimatization process (i.e. that increase in ventilation which lowers the PCO_2) but also from other influences such as metabolism and dead space ventilation. Therefore we sought a better way to assess the rate and magnitude of acclimatization. If we obtained at low altitude the relation of the fall in PCO_2 as the arterial oxygen saturation was lowered during hypoxia (no CO_2 added) then that relation could be used as a standard for judging the acclimatization at high altitude. We found that some subjects moved from their low altitude "standard" line very quickly in the direction of a lower PCO_2 . These appeared to be rapid acclimatizers, and they also showed the most complete acclimatization (in terms of PCO_2 and SaO_2) over the 5 day period. Others moved from their "standard" line to

higher values of PCO_2 and these showed the poorest acclimatization over 5 days (in terms of PCO_2 and SaO_2). We considered that we had a more sensitive measure of acclimatization than has previously been available.

The rapid and the slow acclimatizers were not predicted from their low altitude measurements, but they were quickly identified at high altitude. The implication of these results is that first a lowered CO_2 appears to be an important first step in acclimatization. Second the possibility exists that at low altitude, one could maintain hypoxia for several minutes, or perhaps a half an hour and by tracking how the PCO_2 moves, one could establish a very good predictive test of rapid and slow acclimatizers. These findings are in preparation for publication; specific details of the manuscript are available through the Principal Investigator.

Publications Supported by Contract:

Moore, L.G., S.Y. Huang, R.E. McCullough, J.B. Sampson, J.T. Maher, J.V. Weil, R.F. Grover, J.K. Alexander, and J.T. Reeves. Variable inhibition by falling CO₂ of hypoxic ventilatory response in man. J. Appl. Physiol. (In press).

Huang, S.Y., J.K. Alexander, R.F. Grover, J.T. Maher, R.E. McCullough, R.G. McCullough, L.G. Moore, J.B. Sampson, J.V. Weil and J.T. Reeves. Hypocapnia and sustained hypoxia blunt ventilation on arrival at high altitude. J. Appl. Physiol. (In press).

Submitted for Publication:

Huang, S.Y., J.K. Alexander, R.F. Grover, J.T. Maher, R.E. McCullough, R.G. McCullough, L.G. Moore, J.T. Reeves, J.B. Sampson, and J.V. Weil. Increased metabolism and dead space as components of ventilation at high altitude.

Huang, S.Y., D.P. White, N.J. Douglas, L.G. Moore, R.E. McCullough, J.V. Weil, and J.T. Reeves. Respiratory function in normal chinese: comparison with caucasians.

In Preparation:

Huang, S.Y., J.K. Alexander, R.F. Grover, J.T. Maher, R.E. McCullough, R.G. McCullough, L.G. Moore, J.T. Reeves, J.B. Sampson, and J.V. Weil. Individual variability in acclimatization to high altitude.

Contract Supported Personnel:

Shao Yung Huang, M.D.,
Visiting Scholar from The Shanghai Academia Sinica

Appendix "A"

VENTILATORY RESPONSE TO POIKILOCAPNIC HYPOXIA. L.G. MOORE, S-Y HUANG*, R.E. McCULLOUGH, J.B. SAMPSON*, J.T. MAHER, J.V. WEIL, R.F. GROVER, and J.T. REEVES.
CVP RSCH LAB, UNIV. COLO. HLTH. SCI. CNTR., and DENVER CAMPUS, DENVER, CO 80262

BECAUSE THE INCREASE IN VENTILATION DURING HYPOXIA IS BLUNTED BY RESULTANT HYPOCAPNIA, VENTILATORY RESPONSE TO HYPOXIA IS MEASURED ISOCAPNICALLY. HOWEVER, THE ISOCAPNIC RESPONSE MAY NOT BE RELEVANT IN SITUATIONS SUCH AS ACUTE HIGH ALTITUDE EXPOSURE WHERE HYPOXIA CO-EXISTS WITH CHANGING CO₂. WE SOUGHT TO INVESTIGATE THE RELATIVE CONTRIBUTIONS OF VENTILATORY SENSITIVITY TO O₂ AND CO₂ IN DETERMINING HYPOXIC VENTILATORY RESPONSE WITHOUT CO₂ ADDITION (POIKILOCAPNIA). VENTILATORY RESPONSES TO POIKILOCAPNIC WERE LESS THAN THAT TO ISOCAPNIC HYPOXIA ($\Delta V_e / \Delta S O_2 = .32 \pm .05$ vs $.56 \pm .09$, $P < .05$) BUT WERE CLOSELY CORRELATED ($r = .77$, $P < .001$). TO DETERMINE WHETHER THE REDUCTION IN POIKILO-COMPARED TO ISOCAPNIC HYPOXIA RESPONSES WAS DUE TO INHIBITORY EFFECTS OF HYPOCAPNIA, WE CORRELATED THEIR DIFFERENCES WITH THE VENTILATORY RESPONSE TO CO₂. ALTHOUGH THE CO₂ RESPONSE WAS MEASURED DURING HYPERCAPNIA, THE DIFFERENCE BETWEEN THE ISO- AND POIKILOCAPNIC HYPOXIC RESPONSES CORRELATED WITH THE CO₂ DRIVES ($r = .78$, $P < .001$). THAT IS, THE DEPRESSION OF HYPOXIC RESPONSE UNDER POIKILO- COMPARED TO ISOCAPNIA OCCURRED IN SUBJECTS WITH HIGH CO₂ DRIVES BUT NOT IN SUBJECTS WITH LOW CO₂ DRIVES. WE CONCLUDE THAT THE VENTILATORY RESPONSES TO POIKILOCAPNIC HYPOXIA REFLECT VARIATION IN SENSITIVITY TO HYPOXIA MODULATED BY SENSITIVITY TO CO₂ IN PERSONS WITH HIGH BUT NOT IN THOSE WITH LOW CO₂ DRIVES. (SUPPORTED BY NIH LBI 14985, ARMY CONTRACT DAMD 17-81-C-1051).

- Proc. Soc. Exp. Bio. Med. 739, 1983.

Appendix "B"

VENTILATION AT REST AND EXERCISE AT HIGH ALTITUDE CAN BE PREDICTED FROM HYPOXIC VENTILATORY DRIVES MEASURED AT LOW ALTITUDE. J.T. Reeves**, J.K. Alexander**, R.F. Grover**, S.Y. Huang*, J.T. Maher*, R.E. McCullough*, L.G. Moore*, J.B. Sampson*, and J.V. Weil**. University of Colorado, Denver, CO and Baylor University, Houston TX, Schools of Medicine, and U.S. Army Research Institute for Environmental Medicine, Natick MA.

"Prediction" of ventilation at high altitude might yield insight into ventilatory adaptation to high altitude. In the 11 subjects studied, isocapnic hypoxic ventilatory drive at rest (ISO, rest) measured in Denver, 1600 M, related (Table) to resting but not exercising (450 kpm) ventilation during 5 days on Pikes Peak, 4300 M. The poikilocapnic hypoxic ventilatory drive ($P_{A}CO_2$ allowed to fall) at rest in Denver (Poik, rest) related to exercise but not resting ventilation on Pikes Peak. A poikilocapnic hypoxic drive during exercise in Denver (Poik, Ex) related to ventilation during the same exercise 5 days on Pikes Peak. Symptoms of altitude sickness during the 5 day on Pikes Peak related to poikilocapnic drives in Denver ($P < .05$).

	1	2	3	4	5	Correlations ($P < .05 = *$) of
	Resting Ventilation					tests in Denver with resting
Iso, Rest	.08	*	-	*	*	and exercise ventilation during
Poik, Rest	-	-	-	-	-	5 days on Pikes Peak. The
	Exercise Ventilation					isocapnic test "predicted"
Iso Rest	-	-	-	-	*	resting but not exercise ven-
Poik Rest	-	*	*	*	*	tilation, and the poikilocap-
Poik Ex.	*	*	*	*	*	nic test "predicted" exercise,
						but not resting ventilation.

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